REMARKS

Request for One-Month Extension of Time

Applicant hereby request one-month extension of time, thereby extending the time of responding to the December 16, 2003 Office Action to April 16, 2004. The Office is hereby authorized to charge the $55.00 official fee for such request is to the credit card specified in the Credit Card Payment Form enclosed herewith.

Information Disclosure Statement

In the December 16, 2003 Office Action, the Examiner stated that four foreign language documents cited in the January 31, 2002 Information Disclosure Statement, which include EP0667352, EP0530173, JP11049611, and JP11032795, were not considered due to lack of English translation, abstract, or explanation of relevance.

Enclosed herewith in **Appendix B** are the respective English abstracts of these four documents, as provided by the European Patent Office's patent database. Submission of such English abstracts fulfill the requirements for concise explanation of relevance for documents in foreign language under the provisions of the Manual of Patent Examining Procedure §609(III)(A)(3) (600-122).

Applicant therefore requests the Examiner to consider the above-listed documents in further proceedings.

Response to Objections to Claims 51-61, 64-65 and 72

In the December 16, 2003 Office Action, the Examiner objected to claims 51-61, 64-65, and 72 as being of improper dependent form.

In response, Applicant has hereby cancelled claim 72 and amended claims 51-61 and 64-65. A clean copy of all pending claims as amended is enclosed herewith in **Appendix A**.

Specifically, amended claims 51-61 further limits the claimed composition by defining characteristic temperatures of the articles during heating and/or exposure to the proteolytic enzyme. Therefore, claims 51-61 as amended are now in proper dependent form.

Claim 64 has been rewritten in independent form, as suggested by the Examiner, and claim 65 has been amended to depend from claim 65. Therefore, claims 64 and 65 are now in proper form.

Response to §112 Rejections

The Examiner rejected claims 39-41, 44-53, and 56-62 for lack of enablement under 35 U.S.C. §112, first paragraph.

Specifically, the Examiner asserted that the specification of the instant application does not enable a system capable of disinfecting the article at temperatures of less than 100°C with exposure to *any* proteolytic enzyme.[1] Referring to the Bolton reference, the Examiner stated that treatment of prion protein with less than 100°C would not render the protein susceptible to *all* proteases, and a person ordinarily skilled in the art would therefore have to discover for themselves which proteases are and are not capable of degrading prion proteins that have not been heated to 100°C (see Office Action, page 5, lines 13-22, and page 6, lines 1-7).

In response, Applicant has hereby cancelled claim 62 and amended claim 39.

The amended claim 39, from which claims 40-41, 44-53, and 56-61 depend, recites:

> "A system for disinfecting articles that are susceptible to contamination by infectious prion protein, said system comprising:
>
> (a) said articles;
>
> (b) means for heating said articles to a sufficient temperature and for sufficient time to enhance the proteolytic susceptibility of infectious prion protein associated with said articles;

[1] The Examiner has conceded that the specification of the instant application is enabling with respect to reduction of prion protein on an article by "heating it with a heating means to a temperature range of 100° to about 150°C and then exposing it to a proteolytic enzyme" (see the December 16, 2003 Office Action, page 4, paragraph 9, lines 2-4).

(c) **a proteolytic enzyme selected from the group consisting of keratinases and subtilisins**; and

(d) means for exposing said articles to said proteolytic enzyme,

wherein said system is devoid of chemical selected from the group consisting of sodium hydroxide and sodium hypochlorite."

Enclosed herewith is the Affidavit of Dr. Jason C.H. Shih, attesting to empirical work conducted at his direction showing the efficacy of proteolytic enzyme species such as keratinase and subtilisin in destructing and reducing infectious prion protein at pre-heating temperature of less than 100°C.

Specifically, five (5) different pre-heating temperatures were employed, which included **50°C, 80°C, 90°C, 100°C, and 115°C**, for testing the efficacy of **purified keratinase, subtilisin, and crude keratinase enzymes** at various concentrations in degrading and reducing infectious prion protein that is responsible for the Chronic Wasting Disease in deer and elk. Subtilisin at 200 mg/L was effective in destructing about 83-84% of prion protein after preheating at about 50°C, while crude PWD-1 keratinase at 200mg/L was effective in destructing about 62-84% of prion protein after preheating at about 50°C. Further, the prion concentrations were found to decrease in general with the increase in enzyme concentration, when the same type of enzyme species and the same pre-heating temperature were employed.

Therefore, **Applicant has demonstrated that keratinases and subtilisins are effective in degrading and reducing infectious prion protein at temperatures much lower than 100°C (e.g., 50°C), in consummation with the claim scope of the amended claims 39-41, 44-53, and 56-61**.

The Examiner is respectfully requested to withdraw the enablement rejections against such claims.

In the December 16, 2003 Office Action, the Examiner rejected claims 64-65 for lack of enablement under 35 U.S.C. §112, first paragraph, on the basis that the specification does not reasonably provide enablement for systems using only enzymatically active fragments of the *Bacillus licheniformis* PWD-1 keratinase.

Applicant respectfully disagrees.

The case law provides that a patent need not teach, and preferably omits, what is *well known* in the art. *In re Buchner*, 929 F.2d 1367 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). The claimed invention only needs to be enabled so that any person skilled in the art can make and use the invention without *undue experimentation*. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988), and the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498 (CCPA 1976).

In this case, the well-known technology of incremental truncation[2] can be used to generate a fragment library containing all possible fragments of the *Bacillus licheniformis* PWD-1 keratinase, which can be systematically scanned for protease activity via routine experimentation and from which active fragments of the keratinase can be readily determined by a person ordinarily skilled in the art.

Therefore, **determination of active fragments of the *Bacillus licheniformis* PWD-1 keratinase does not require undue experimentation, and a person ordinarily skilled in the art can readily practice the claimed invention** as recited in claims 64 and 65, based on disclosure in the instant specification as well as the state of art at the time when the present application was filed.

In the December 16, 2003 Office Action, the Examiner rejected claims 81 and 83 for introducing new matter.

In response, Applicant has hereby cancelled claims 81 and 83.

Response to §103 Rejections

The Examiner rejected claims 39-65, 71-74, and 80-83 under 35 U.S.C. §103(a) as being obvious over the primary reference World Health Organization (hereinafter "WHO") document, in view of numerous secondary references including Huth et al. U.S. Patent No. 6,448,062 (hereinafter "Huth"), Vlass et al. U.S. Patent No. 6,210,639 (hereinafter "Vlass"), Potgeiter et al. U.S. Statutory Invention Registration No. H1,818 (hereinafter "Potgeiter"), Shih U.S. Patent No.

[2] See Ostermeier et al., Combinatorial Protein Engineering by Incremental Truncation, PROC. NATL. ACAD. SCI. USA, vol. 96, pp 3562-3567 (March 1999).

5,171,682 (hereinafter "Shih"), Bolton et al., Molecular Characteristics of the Major Scrapie Prion Protein (hereinafter "Bolton"), Oesch et al. Properties of the Scrapie Prion Protein: Quantitative Analysis of Protease Resistance (hereinafter "Oesch"), Darbord, Inactivation of Prions in Daily Medical Practice (hereinafter "Darbord"), Taylor et al., Inactivation the Bovine Spongiform Encephalophathy Agent by Rendering Procedures (hereinafter "Taylor"), and/or Belhumeur et al. WO 00/65344 (hereinafter "Belhumeur").

In response, Applicant has cancelled claims 62, 72, 81, and 83, and amended claims 39, 64, 71, 80, and 82.

Applicant hereby traverses the Examiner's rejections, for the following reasons:

Amended claim 39, from which claims 40-61 and 63 depend, recites:

> "A system for disinfecting articles that are susceptible to contamination by infectious prion protein, said system comprising:
>
> (a) **said articles, characterized by a first temperature of not exceeding about 150°C during a first duration, and a second temperature of at least 40°C during a second, subsequent duration**;
>
> (b) means for heating said articles during said first duration to said first temperature and for sufficient time to enhance the proteolytic susceptibility of infectious prion protein associated with said articles;
>
> (c) a proteolytic enzyme selected from the group consisting of keratinases and subtilisins; and
>
> (d) means for **exposing said articles to said proteolytic enzyme at said second temperature during said second, subsequent duration**."

Amended claims 64 (from which claim 65 depends), 71 (from which claims 73-74 depend), 80, and 82 recite corresponding limitations as highlighted hereinabove.

It is clear that the claimed invention of the present application requires that **the contaminated articles be treated be characterized by an elevated temperature of at least 40°C during proteolytic enzyme digestion, subsequent to the preheating**.

In contrast, **the primary reference cited by the Examiner, i.e., the WHO document,** only discloses sterilization of prion-contaminated surgical instruments by boiling or autoclaving with sodium hydroxide or sodium hypochlorite, followed by **subsequent routine sterilization** (see page 29, Appendix III, section 2 of the WTO document).

Nothing in the primary reference, i.e., the WHO document, teaches or suggests that the subsequent routine sterilization involves enzyme digestion, much less enzyme digestion at elevated temperatures.

The Examiner in the December 16, 2003 Office Action conceded that the primary reference WHO document fails to teach use of proteolytic enzyme for sterilization purposes, but attempted to remedy such deficiency of such WHO document by citing multiple secondary references including Huth, Vlass, Potgeiter, Bolton, Oesch, Shih, Darbord, Tayler, and Belhumeur.

However, **none of the secondary references teach or suggest the use of proteolytic enzyme at elevated temperatures of at least 40°C in cleaning surgical instruments or like articles**. More importantly, none of the secondary reference appreciates the advantages of using elevated temperatures during the enzyme digestion, and therefore does not provide motivation for a person ordinarily skilled in the art to do so.

Instead, **Potgeister teaches reduction of temperature to ambient before addition of the enzymes** (see Potgeister, column 21, line 67 and column 22, lines 1-2), and **Bolton teaches cooling of the treated material before addition of the proteinase K** (see Bolton, page 5901, right column, Figure 2, lines 9-10).

Therefore, the Examiner's hypothetical combination of the secondary references with the primary references fails to establish a *prima facie* case of obviousness.

Thus, pending claims 39-61, 63-65, 71, 73-74, 80, and 82 are patentably distinguished over all the cited references.

The Examiner is hereby requested to reconsider, and upon reconsideration, to withdraw the rejections of claims 39-61, 63-65, 71, 73-74, 80, and 82.

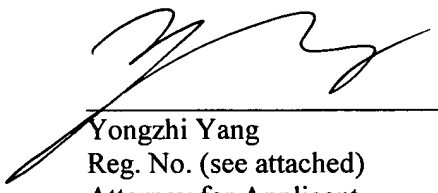
CONCLUSION

Based on the foregoing, claims 39-61, 63-65, 71, 73-74, 80, and 82 as amended are in form and condition for allowance. Claims 62, 66-67, 70, 72, 81, and 83 have been cancelled, and method claims 1-38, 68-69, and 75-79 are current withdrawn from consideration, awaiting rejoinder upon allowance of the corresponding product claims.

The Office is hereby authorized to charge $98.00, which includes the $55.00 fee for one-month extension of time and the $43.00 fee for rewriting claim 64 into independent form, to the credit card specified in the Credit Card Payment Form enclosed herewith.

Additionally, the Office is hereby authorized to charge any deficiency and to credit any overpayment to Deposit Account No. 08-3284 of Intellectual Property/Technology Law.

Respectfully submitted,



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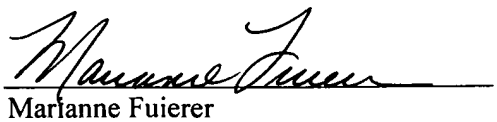

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APPENDIX A

Clean Copy of All Pending Claims

1. A method of disinfecting article(s) that are susceptible to contamination by infectious prion protein, the method comprising the steps of:

   (a) heating said article(s) to a sufficient temperature and for sufficient time to enhance the proteolytic susceptibility of infective prion protein associated with said article(s); and

   (b) exposing the heated article(s) to a proteolytic enzyme that is effective for at least partial reduction of the infective protein prion associated with said article(s).

2. The method of claim 1, wherein said articles comprise surgical instruments.

3. The method of claim 2, wherein said surgical instrument(s) are selected from the group consisting of: clamps, forceps, scissors, knives, cables, punches, tweezers, cannulae, calipers, carvers, curettes, scalers, dilators, clip applicators, retractors, contractors, excavators, needle holders, suction tubes, trocars, coagulation electrodes, electroencephalographic depth electrodes, rib and sternum spreaders, bipolar probes, and rib shears.

4. The method of claim 1, wherein said article(s) comprise cutleries and kitchen utensils.

5. The method of claim 4, wherein said cutleries and kitchen utensils are selected from the group consisting of: knives, forks, scissors, peelers, parers, slicers, spatulas, and cleavers.

6. The method of claim 1, wherein said article(s) comprise laboratory apparatus(es).

7. The method of claim 6, wherein said laboratory apparatus(es) are selected from the group consisting of: containers, filtration devices, centrifuges, spectrophotometers, and fluorometers.

8. The method of claim 1, wherein said article(s) comprise veterinary devices.

9. The method of claim 8, wherein said veterinary devices are selected from the group consisting of clamps, forceps, knives, saws, probes, and electronic stun equipment.

10. The method of claim 1, wherein the temperature in step (a) comprises a temperature not exceeding about 150°C.

11. The method of claim 1, wherein the temperature in step (a) comprises a temperature of at least 35°C.

12. The method of claim 1, wherein the temperature in step (a) comprises a temperature below about 150°C.

13. The method of claim 1, wherein the temperature in step (a) comprises a temperature in a range of from about 100°C to about 150°C.

14. The method of claim 1, wherein the temperature in step (a) comprises a temperature in a range of from about 125°C to about 140°C.

15. The method of claim 1, wherein step (b) is conducted at lower temperature than step (a).

16. The method of claim 1, wherein step (b) is carried out at temperature above about 40°C.

17. The method of claim 1, wherein step (b) is carried out at temperature above about 50°C.

18. The method of claim 1, wherein step (b) is carried out at temperature in a range of from about 35°C to about 75°C.

19. The method of claim 1, wherein step (b) is carried out at temperature in a range of from about 40°C to about 75°C.

20. The method of claim 1, wherein step (b) is carried out at temperature in a range of from about 50°C to about 65°C.

21. The method of claim 1, wherein the proteolytic enzyme comprises at least one enzyme selected from the group consisting of keratinase enzymes, proteinase K, trypsins, chymotrypsins, pepsins, chymosins, cathepsins, subtilisins, elastases, collagenases, endopeptidases, peptidases, oligopeptidease, thermolysins, bacillolysin, mycilysins, carboxypeptidases, leucyl aminopeptidases, aminopeptidases, extremthermophilic proteases, carbonyl hydrolase, papain, pancreatin, streptokinase, streptodornase, ficin, carboxypeptidase, chymopapain, and bromelin.

22. The method of claim 1, wherein the proteolytic enzyme comprises a keratinase enzyme.

23. The method of claim 1, wherein the proteolytic enzyme comprises an active fragment of a keratinase enzyme.

24. The method of claim 1, wherein the proteolytic enzyme comprises a Bacillus licheniformis PWD-1 enzyme or an active fragment thereof.

25. The method of claim 1, wherein the proteolytic enzyme comprises a protease enzyme.

26. The method of claim 25, wherein the protease enzyme comprises a carbonyl hydrolase.

27. The method of claim 26, wherein the carbonyl hydrolase comprises subtilisin.

28. The method of claim 27, wherein the subtilisin comprises a mutant of wild-type Bacillus amyloliquefaciens subtilisin, comprising one or more amino acid substitutions, additions, or deletions.

29. The method of claim 25, wherein the protease enzyme comprises at least one enzyme selected from the group consisting of: papain, pancreatin, trypsin, chymotrypsin, pepsin, streptokinase, streptodornase, ficin, carboxypeptidase, aminopeptidase, chymopapain, bromelin, and subtilisin.

30. A method of removing infective prion protein from a surgical instrument contaminated with same, the method including (a) heating the surgical instrument at a temperature in a range of from about 100°C to about 150°C, followed by (b) exposing the heated surgical instrument to a proteolytic enzyme at a temperature in a range of from about 35°C to about 100°C at which the proteolytic enzyme is thermally stable and proteolytically effective to at least partially destroy the infective prion protein contaminating said surgical instrument.

31. The method of claim 30, wherein said heating is conducted for a time of from about 5 minutes to about 5 hours.

32. The method of claim 30, wherein the proteolytic enzyme comprises at least one enzyme selected from the group consisting of keratinase enzymes, proteinase K, trypsins, chymotrypsins, pepsins, chymosins, cathepsins, subtilisins, elastases, collagenases, endopeptidases, peptidases, oligopeptidease, thermolysins, bacillolysin, mycilysins, carboxypeptidases, leucyl aminopeptidases, aminopeptidases, extremthermophilic proteases, carbonyl hydrolase, papain, pancreatin, streptokinase, streptodornase, ficin, carboxypeptidase, chymopapain, and bromelin.

33. The method of claim 30, wherein the proteolytic enzyme comprises *Bacillus licheniformis* PWD-1 keratinase.

34. The method of claim 1, wherein the proteolytic enzyme comprises a protease enzyme.

35. The method of claim 34, wherein the protease enzyme comprises a carbonyl hydrolase.

36. The method of claim 35, wherein the carbonyl hydrolase comprises subtilisin.

37. The method of claim 36 , wherein the subtilisin comprises a mutant of wild-type Bacillus amyloliquefaciens subtilisin, comprising one or more amino acid substitutions, additions, or deletions.

38. The method of claim 34, wherein the protease enzyme comprises at least one enzyme selected from the group consisting of: papain, pancreatin, trypsin, chymotrypsin, pepsin, streptokinase, streptodornase, ficin, carboxypeptidase, aminopeptidase, chymopapain, bromelin, and subtilisin.

39. A system for disinfecting articles that are susceptible to contamination by infectious prion protein, said system comprising:

(a) said articles, characterized by a first temperature of not exceeding about 150°C during a first duration, and a second temperature of at least 35°C during a second, subsequent duration;

(b) means for heating said articles during said first duration to said first temperature and for sufficient time to enhance the proteolytic susceptibility of infectious prion protein associated with said articles;

(c) a proteolytic enzyme selected from the group consisting of keratinases and subtilisins; and

(d) means for exposing said articles to said proteolytic enzyme at said second temperature during said second, subsequent duration.

40. The system of claim 39, wherein the proteolytic enzyme comprises keratinase.

41. The system of claim 40, wherein the keratinase is provided in a solution at a concentration within a range of from about 0.2 g/L to about 1.0 g/L.

42. The system of claim 41, wherein the solution comprises a solvent selected from the group consisting of distilled water, alcohol, buffer solution, and detergent solution.

43. The system of claim 42, wherein said solution further comprises one or more chemical additives selected from the group consisting of surfactants, builders, boosters, and fillers.

44. The system of claim 39, wherein said articles comprise surgical instruments.

45. The system of claim 44, wherein said surgical instrument(s) are selected from the group consisting of: clamps, forceps, scissors, knives, cables, punches, tweezers, cannulae, calipers, carvers, curettes, scalers, dilators, clip applicators, retractors, contractors, excavators, needle holders, suction tubes, trocars, coagulation electrodes, electroencephalographic depth electrodes, rib and sternum spreaders, bipolar probes, and rib shears.

46. The system of claim 39, wherein said articles comprise cutleries and kitchen utensils.

47. The system of claim 46, wherein said cutleries and kitchen utensils are selected from the group consisting of: knives, forks, scissors, peelers, parers, slicers, spatulas, and cleavers.

48. The system of claim 39, wherein said articles comprise laboratory apparatuses.

49. The system of claim 39, wherein said article(s) comprise veterinary devices.

50. The system of claim 49, wherein said veterinary devices are selected from the group consisting of clamps, forceps, knives, saws, probes, and electronic stun equipment.

51. The system of claim 39, wherein said first temperature is higher than said second temperature.

52. The system of claim 39, wherein said first temperature is at least about 35°C.

53. The system of claim 39, wherein said first temperature is at least about 60°C.

54. The system of claim 39, wherein said first temperature is in a range of from about 100°C to about 150°C.

55. The system of claim 39, wherein said first temperature is at least about 75°C.

56. The system of claim 39, wherein the first temperature is the same as the second temperature.

57. The system of claim 39, wherein the second temperature is above about 40°C.

58. The system of claim 39, wherein the second temperature is above about 50°C.

59. The system of claim 39, wherein the second temperature is in a range of from about 35°C to about 75°C.

60. The system of claim 39, wherein the second temperature is in a range of from about 40°C to about 75°C.

61. The system of claim 39, wherein the second temperature is in a range of from about 50°C to about 65°C.

63. The system of claim 39, wherein the proteolytic enzyme comprises a keratinase enzyme.

64. A system for disinfecting articles that are susceptible to contamination by infectious prion protein, said system comprising:

(a) said articles, characterized by a first temperature of not exceeding about 150°C during a first duration, and a second temperature of at least 35°C during a second, subsequent duration;

(b) means for heating said articles during said first duration to said first temperature and for sufficient time to enhance the proteolytic susceptibility of infectious prion protein associated with said articles;

(c) an active fragment of a keratinase enzyme that is effective for at least partial reduction of the infectious prion protein associated with said articles; and

(d) means for exposing said articles to said active fragment of the keratinase enzyme at said second temperature during said second, subsequent duration.

65. The system of claim 64, wherein the active fragment of the keratinase enzyme comprises an active fragment of a Bacillus licheniformis PWD-1 enzyme.

68. The system of claim 39, wherein the proteolytic enzyme comprises subtilisin.

69. The system of claim 68, wherein the subtilisin comprises a mutant of wild-type Bacillus amyloliquefaciens subtilisin, comprising one or more amino acid substitutions, additions, or deletions.

71. A system for removing infective prion protein from a surgical instrument contaminated with same, the system comprising (a) said surgical instrument, characterized by a first temperature in a range of from about 100°C to about 150°C during a first duration, and a second temperature in a range of from about 35°C to about 150°C during a second, subsequent duration; (b) means for heating the surgical instrument to said first temperature during said first duration, (c) a proteolytic enzyme that is thermally stable at a temperature in a range of from about 35°C to about 100°C and proteolytically effective to at least partially destroy the infective prion protein contaminating said surgical instrument, and (d) means for exposing the surgical instrument to the proteolytic enzyme at said second temperature during the second, subsequent duration.

73. The system of claim 71, wherein the proteolytic enzyme comprises at least one enzyme selected from the group consisting of keratinase enzymes, proteinase K, trypsins, chymotrypsins, pepsins, chymosins, cathepsins, subtilisins, elastases, collagenases, endopeptidases, peptidases, oligopeptidease, thermolysins, bacillolysin, mycilysins, carboxypeptidases, leucyl aminopeptidases, aminopeptidases, extremthermophilic proteases, carbonyl hydrolase, papain, pancreatin, streptokinase, streptodornase, ficin, carboxypeptidase, chymopapain, and bromelin.

74. The system of claim 71, wherein the proteolytic enzyme comprises *Bacillus licheniformis* PWD-1 keratinase.

75. The system of claim 71, wherein the proteolytic enzyme comprises a protease enzyme.

76. The system of claim 75, wherein the protease enzyme comprises a carbonyl hydrolase.

77. The system of claim 76, wherein the carbonyl hydrolase comprises subtilisin.

78. The system of claim 77, wherein the subtilisin comprises a mutant of wild-type Bacillus amyloliquefaciens subtilisin, comprising one or more amino acid substitutions, additions, or deletions.

79. The system of claim 75, wherein the protease enzyme comprises at least one enzyme selected from the group consisting of: papain, pancreatin, trypsin, chymotrypsin, pepsin, streptokinase, streptodornase, ficin, carboxypeptidase, aminopeptidase, chymopapain, bromelin, and subtilisin.

80. (Currently amended) A system for disinfecting articles that are susceptible to contamination by infectious prion protein, comprising:

(a) said articles, characterized by a first temperature in a range of from about 35-150°C during a first duration, and a second temperature in a range of about 35-100°C during a second, subsequent duration;

(b) means for heating said articles during said first duration to said first temperature for a sufficient period of time to enhance proteolytic susceptibility of said infective prion protein;

(c) *Bacillus licheniformis* PWD-1 keratinase; and

(d) means for exposing the heated articles to the *Bacillus licheniformis* PWD-1 keratinase at said second temperature during said second, subsequent duration.

82. A system for disinfecting articles that are susceptible to contamination by infectious prion protein, comprising:

(a) said articles, characterized by a temperature in a range of from about 35-100°C;

(b) *Bacillus licheniformis* PWD-1 keratinase; and

(b) means for exposing the articles to *Bacillus licheniformis* PWD-1 keratinase at said temperature for a sufficient period of time to degrade the prion protein.